IRB ADVISOR

YOUR PRACTICAL GUIDE TO INSTITUTIONAL REVIEW BOARD MANAGEMENT

MAY 2019 Vol. 19, No. 5; p. 49-60

INSIDE

RELIAS MEDIA

WHO Calls for International Registry, Oversight of Gene Editing Research

Controversial gene editing raises questions for IRBs

By Gary Evans, Medical Writer

A World Health Organization (WHO) panel formed in the wake of highly controversial human embryo research in China is calling for the creation of a "central registry on human genome editing research to create an open and transparent database of ongoing work."[1]

After an initial two-day meeting in March, the WHO committee agreed "that it is irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing," according to the organization's statement. The panel "has invited all those conducting human genome editing research to open discussions with the committee to better understand the technical environment and current governance arrangements, and help ensure their work meets current scientific and ethical best practice."

> THE WHO COMMITTEE AGREED "THAT IT IS IRRESPONSIBLE AT THIS TIME FOR ANYONE TO PROCEED WITH CLINICAL APPLICATIONS OF HUMAN GERMLINE GENOME EDITING."

Plans call for the committee to gather information from a wide range of sources with the goal of developing recommendations for "a comprehensive governance framework that is scalable, sustainable, and appropriate for use at the international, regional, national, and local levels. The committee will solicit the views of multiple stakeholders including patient groups, civil society, ethicists, and social scientists."

Financial Disclosure: Author **Melinda Young**, Medical Writer **Gary Evans**, Editor **Jill Drachenberg**, Editor **Jesse Saffron**, Editorial Group Manager **Terrey L. Hatcher**, Physician Editor **Lindsay McNair**, MD, MPH, MSBioethics, and Nurse Planner **Kay Ball**, PhD, RN, CNOR, CMLSO, FAAN, report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

IRB ADVISOR

IRB Advisor, *ISSN 1535-2064*, is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *IRB Advisor*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.
GST Registration Number: R128870672.

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The lone U.S. member of the panel is R. Alta Charo, JD, Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin. She declined comment for this story when reached as the panel readied to hold its initial meeting.

In originally forming the panel, WHO stated that "the recent application of tools such as CRISPR-Cas9 to edit the human genome have highlighted the need for the development of standards in this area."[2]

At a meeting in November 2018 in Hong Kong, researcher He Jiankui announced he had genetically modified twin embryos to make them resistant to HIV infection. Although the research community was initially skeptical, a Chinese state media report later confirmed that the gene-edited twins babies had been born.[3] The report noted that Dr. He "seriously violated" regulations and could face charges. The researcher claimed to have used CRISPR-Cas9 to disable the CCR5 gene that makes the protein HIV needs to enter cells. As this issue went to press, the incident remained under investigation by various authorities and there was still some confusion about what exactly had transpired.

"Dr. He says he created two kids. I assume he did, but who knows?" says **Robert Klitzman**, MD, director of the masters of bioethics program at Columbia University in New York City. "I think this WHO panel is needed. There are risks in doing this research now, and one issue is rogue researchers. Someone could do this this in their lab in another country."

There will be those who seek out gene-edited human embryos, opening a path of global dispersement for research conducted without adequate oversight and regulation.

"We have global reproductive travel now," Klitzman says. "There are only three countries where you can buy and sell human eggs, which are Russia, India, and the United States. People come from other countries, and laws vary between countries. If something is offered in a particular country, people may go there to get it done."

The risks of this type of research include "off-target" effects of gene editing. "A researcher may try to take out just one part of a gene but accidently affect other nearby genes. Dr. He has been criticized for not being more precise in the DNA affected," he says.

There also could be unintended consequences if researchers edit a gene without realizing it has more than one function.

"You don't want to be knocking out a gene that causes cancer if it turns out you are going to have [increased risk] of intellectual disabilities," Klitzman says. "We don't know enough about these possibilities, I would argue."

Another issue is long-term effects, which would have to be tracked over time to see whether the gene editing had some downstream consequences for the baby. For example, researchers are looking at the long-term risks of intellectual disabilities in babies born via in vitro fertilization (IVF), he says.

"The baby is born and is OK, but eight years later when they are in the second grade, you start to see problems," Klitzman says. "We need to have follow-up over time once this [gene editing] begins to happen. You don't want to roll this all out at once. We need to be very cautious in doing this research on embryos."

'The Very Core of Who We Are'

Craig Klugman, PhD, is a bioethicist and member of the IRB at DePaul University in Chicago. *IRB Advisor* asked him to comment on the implications of this emerging research for U.S. IRBs. This interview has been edited for length and clarity.

IRB Advisor: How significant is the formation of this WHO oversight panel for human embryos in gene-editing research?

Klugman: It's needed because of Dr. He's announcement. There had been an unofficial moratorium on gestating embryos that might be edited on an international level, and clearly asking people to volunteer to do something was insufficient.

The WHO recognizes that research is going to go ahead and there are a number of groups around the world who are doing gene editing work. At the same time, they recognize that this is a very fundamental issue of importance to all human beings. It is at the very core of who are and what our future will be. We need to look at this from an international perspective. This is not something that a single country is going to be able to say, "In our country, without our political borders, this is what is acceptable and this is what is not." It really does need to be worldwide effort because any [human genome] changes could have repercussions all over the globe.

IRB Advisor: One of the risks cited is genetic changes that can be inherited by future descendants. Is this research on the horizon?

Klugman: That is very likely. In genetic engineering, we say there are two types of cells — somatic cells and germ-line cells. We could take a born person and change a cell in their body on the gene of an organ to make up for a disease state. Maybe they don't produce a [needed] protein or maybe they produce a bad mutation. That could be fixed, and it would just remain in that one individual. But in germ-line engineering, we are changing things in cells that could be passed on to future generations. This is more challenging because in some of the work we are seeing, we don't know if it will be passed on or not, but there is a high likelihood that it will.

IRB Advisor: The WHO is moving rapidly on this, but there is some concern that the proverbial genie is now out of the bottle.

Klugman: There is a lot more international collaboration happening. Even if somebody on your campus or in your institution is not doing this research, they may be working with people who are in other countries. In some sense, there's a lot of national pride in doing research. Now that we know this work is going on in other countries, it is likely more researchers in the U.S. are going to be interested in doing this.

There is a group in Oregon already working on human embryos; they were just not planning to gestate the embryos after the gene editing. There is a group in New York that just announced they were interested in doing this. I think we are going to see that this is an area of research that people more and more are going to jump into in order to see themselves as competitive in the international scientific realm.

IRB Advisor: You note that Dr. He consulted with several researchers — including some in the United States — although they may not have known he was actually going to proceed with gestation of gene-edited embryos. What are the implications of such consultations for IRBs?

Klugman: From what I understand, U.S. IRBs were not involved because no research was conducted at their institutions, nor did the researchers participate in conducting the research in China. They were just consulting on it. Under the regulations we have, you don't have to let an IRB know if you are just consulting because there are no human subjects in consulting. It raises an interesting question. The IRB is about protecting human subjects, so if you are not working with human subjects it doesn't fall under an IRB. Academic freedom says you can work on anything you want, especially if you are just talking ideas with someone. So it's one of those things that, as it happened, would not have fallen under the IRB at the institutions where the consultants were located.

IRB Advisor: With more interest now in this research, is the Common Rule sufficient to prevent such an extraordinary incident from happening here?

Klugman: The short answer is no because under the U.S. rules, an embryo is not considered a human subject. So institutions that do a lot of embryo research have established what are called Embryonic Stem Cell Research Oversight (ESCRO) committees. Those are bodies that do a lot of this work and have been set up, often voluntarily, to take a look at this. But under the Common Rule, these are not human subjects. They are also not animal subjects, so they don't fall under either.

I think IRBs need to — even though it is my understanding the Common Rule does not require them necessarily to review this work — talk to their institution about how to ensure that there is some review in this area.

IRB Advisor: Could this WHO panel resolve this somewhat and

make recommendations that would be helpful in the U.S.?

Klugman: Yes, but remember the Common Rule does not have a great effect outside the United States, so they are probably not going to look at the U.S. specifically. There is only one person from the U.S. on the WHO committee. I think they are going to look at the broader issues of rules and guidelines internationally. I don't think they are going to drill down to the regulatory details because they just can't do that for every international audience.

IRB Advisor: It seems the recent research in China was a call to action.

Klugman: I think the difference here with what we saw in China is if you are doing embryo research — and you are not planning on transplanting it for gestation — it wouldn't fall under the IRB.

What happened in this particular case is the transfer of an edited embryo into a woman who wanted to be a mother. So, there is a question whether that would come under IRB or not because in IVF, there are no human subjects if you are just doing an IVF transfer. Does an edited embryo change that? If it does, it becomes a new way of looking at things that previously were just a clinical judgment.

IRB Advisor: How do you think that conundrum should be interpreted?

Klugman: I would want to see more [IRB] oversight in that circumstance. Doing the work in the laboratory is one thing, but transferring the embryo into a woman for gestation is another step. There is a difference between finding knowledge and creating a human being.

IRB Advisor: This case seems to reinforce the perception that expected research norms can be suddenly exceeded.

Klugman: This is not the first case of research being done that people have questioned. We have our historical examples of human subject research abuses, but it is usually with already-born people. The embryo occupies a strange position, at least in the U.S., where it is not a person but it is more than just a cluster of cells or tissues. How you think about that may depend on your politics and your religious beliefs, with the exception of these ESCROs, which are a great model. I think we are presented with a unique challenge at this point in time. ■

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Preventing Rogue Researchers Should Be on IRBs' Priority List

Watch for red flags of noncompliance

By Melinda Young, Author

Bioethicists and the human research protections industry have been shocked in recent years by reports of rogue researchers carrying out investigations that raise huge red flags and, in some instances, could be regulatory breaches.

In 2018, the scientific world learned that a Chinese investigator claimed his research resulted in genetically edited newborn twins. He also claimed his research was approved by a Chinese ethics board. *(For more information, see story in the January 2019 issue of* IRB Advisor.*)*

In 2017, William Halford, PhD, a professor at Southern Illinois University School of Medicine, had conducted herpes clinical trials on the island of St. Kitts. Halford died that year from a rare cancer, leaving behind his research and its controversial way of circumventing regulatory safeguards. He had not gotten his research approved by the university's IRB, according to university officials interviewed by *IRB Advisor* in 2017 but who have not responded to follow-up interview requests. *(See story about Halford's research in the November 2017 issue of* IRB Advisor.*)*

While these are two highly publicized examples of potential ethical and regulatory breaches, they are part of a trend, says **Joseph Crossno**, MS, CPIA, assistant director in the office of research compliance at Central Michigan University in Mt. Pleasant.

"In 2015, we started getting anecdotal reports and seeing stories in the press regarding research — either approved or unethical research — being conducted in various places around the country," he says.

Crossno recalls seeing social media reports from researchers about studies they had started at another university but continued with after they left, possibly without informing their IRBs.

"It had us asking the question, 'Could this happen here?' And if it did, what was the likelihood we would know in time to do something about it?" he says.

These concerns prompted Crossno to help lead an effort to develop standard operating procedures that could help prevent rogue research.

"We started monitoring social media outlets, including Facebook, Twitter, LinkedIn," he says. "Some people were advertising things on other platforms for a time, but Facebook was the popular one with human subject research for recruitment and advertising."

The goal behind the monitoring was to check on what the IRB had approved for a study and then see whether the investigator was recruiting or advertising the study as had been approved by the IRB, says **Robert S. Bienkowski**, PhD, CIP, CHRC, director of the office of research compliance at Central Michigan University. *(See story on IRBs and recruitment ads, right.)*

"It's reasonable to ask the question, 'How do you know unapproved research is not going on at your university?'" Bienkowski says. "A careless administrator might say, 'You just don't know, and we haven't seen any pictures or stories in the media, so we just don't know.'"

By starting a process of surveillance and monitoring, a research institution can discover potential breaches and problems, he adds.

"In classic compliance processes, you ask about the risks to the institution, including the risk of the institution's reputation, and then you develop a process to address the risk," Bienkowski explains.

The Central Michigan University research compliance office conducts surveillance, looking for unknown problems. "We don't know what

RESEARCHERS' ADVERTISING CAN FALL INTO NONCOMPLIANCE

One common area of noncompliance in human subjects research involves advertising and recruitment materials.

Investigators might begin to market their study to potential participants even before they have received IRB approval, or make changes to their advertising and recruitment materials after an original version and format were approved. In both cases, the investigators are noncompliant.

"The informed consent process begins with recruitment," says **Joseph Crossno,** MS, CPIA, assistant director in the office of research compliance at Central Michigan University in Mt. Pleasant. "If you mislead participants in recruitment and they go into a study thinking they're going to be doing one thing, then there's a problem."

"Not all participants thoroughly read the consent document, so there is a problem of the recruitment material not matching what's in the consent form," he adds. "When you explain that to researchers, they understand that advertising has to match what's said in the consent form or there is the possibility of participants not understanding."

Researcher education includes a two-page paper titled "Why does the IRB care about advertising?" It explains how the IRB views advertising of an approved protocol to be the beginning of the informed consent process, shared with *IRB Advisor* by Crossno and Central Michigan University.

According to the CMU educational sheet, the following is the information that recruitment advertisements should include:

- investigator's and/or research facility's name and address;
- research purpose and study condition;
- summary of eligibility criteria;
- brief list of benefits;
- subjects' time and other commitments;
- research location and contact information.

The investigator education also asks that researchers do not use coercive or misleading language or graphics, imply a guarantee of benefits, claim the study product is safe or effective, or emphasize free treatment.

Researchers that tweak their marketing materials in hopes of drawing more attention to their study do not understand that by changing it, they might be dropping something that is required in the regulations, Crossno says.

"Sometimes, it's as simple as, 'I can't fit it on the page,'" he explains. "So they cut things out that they think are unimportant, and it turns out those things are important." ■

it is, but we know it's out there," Bienkowski says.

The program found that most noncompliance issues involved unapproved changes in recruitment materials, Crossno says.

Surveillance is a proactive way to monitor research compliance, including recruitment advertising and marketing.

"We designed the surveillance as a very simple, not labor-intensive program," Crossno says. "We made it as simple as possible to start and planned to tweak things and ramp up the program as we go along."

For instance, the surveillance program uses automatic electronic search alerts, such as Google Alerts.

"We put in half a dozen search terms and get automatic reminders," Crossno says. "To start, I put in 'research' and 'Central Michigan University,' and that generated a lot of hits. I'd spend all day looking through the returns."

Now, Crossno uses keywords that are more refined, based on the results they saw in the first few years of the surveillance program. This resulted in findings of mostly minor noncompliance, he adds.

For example, surveillance sometimes finds problems with student-initiated studies in recruitment and advertising. Often, these are cases of student-initiated research in which the advertising either wasn't approved by the IRB, or it was approved and later modified in a way that removed key elements, Crossno explains.

"All of these findings have been minor noncompliance," he says.

Sometimes, researchers will talk about their research plans on a blog, outlining their plans for the months ahead. If their blog description doesn't match what they submitted in a proposal to the IRB, Crossno will reach out to the faculty researcher, student researcher, and faculty adviser and say, "You'll need to modify your protocol if you're really going to do this," he says.

"I try, almost exclusively, to go through the faculty member," Crossno says. "Sometimes, we'll contact a student but copy the faculty member."

THE PROGRAM FOUND THAT MOST NONCOMPLIANCE ISSUES INVOLVED UNAPPROVED CHANGES IN RECRUITMENT MATERIALS.

If Crossno knows the student investigator, he might include the student on the email message, writing, "You posted this flier on this platform, and I just wanted to make sure you and Dr. So-and-So are aware this is not the approved version."

When investigators take actions in their studies that an IRB has not approved, it is protocol drift, Bienkowski says.

Researchers sometimes do not understand that the IRB has to see everything that will be shown to participants, including changes to the size of font, color, layout of recruitment materials, and so forth, he explains.

These instances of noncompliance found through surveillance often involve minor changes to what investigators presented to the ethics board. From the researcher's perspective, these changes seem trivial: "There is a factor of 'Do I really have to go back to the IRB to say I reformatted the original application, and it looks better now?'" Bienkowski says. "But yes, they do."

When noncompliance occurs, whether minor or serious, the situation is brought to the attention of the oversight committee, including the IRB if it is human subjects research, Bienkowski says. "The chair of the committee will make an initial determination," he adds.

One example of a noncompliant study advertisement involves a case in which the investigator placed a banner in front of the student union. The banner advertised participation in the survey and emphasized participant compensation, the dates of the study, and how participants would be contacted and what they had to do, Crossno says.

"The problem was the study wasn't approved yet, and the emphasis was on compensation. The principal investigator's name and location were missing," he explains. "That was an example of one that was definitely noncompliant, and we referred it to the IRB chair."

Since it was minor noncompliance and there was no impact on subject risks, it could be handled by the IRB chair, Crossno notes.

"Because advertisements had become such a recurring issue, the chair asked me to give a talk at the convened IRB about advertisements and what had to be included and excluded," Crossno says. "So when the IRB reviews advertising and recruitment materials, this gives them a checklist and reminder with quick bullet points of what they need to look for."

Compliance monitoring involves collecting data, but this does not have to be an exhaustive process. "One thing we did to keep our version of this program simple is I

don't invest a significant amount of time tracking statistics," Crossno says. "I take snapshots over brief periods of time."

The program also relies on communication and retraining/education of researchers and their faculty advisers.

"I sit down with a faculty member or student and say, 'Here's what we found. Here's what's required. Here's what you did, and in the future, you need to make sure you do what's required,'" Crossno says. "These are not hostile sessions; we just assess the researcher's level of understanding, and they learn what is needed going forward." ■

Is It Standard of Care, Research, or Something Else?

Tips on how to decide

Researchers and IRBs sometimes have questions about studies and treatment that fall in the gray area between research and personalized medical care. Is it innovative care that is intended to benefit a specific patient — or an innovation that has the potential of being generalizable?

Another question to ask is whether the intent is to practice nationally or broadly in a specific discipline, says **Jeremy Corsmo**, MPH, senior director of research compliance and regulatory affairs at Cincinnati Children's Hospital, and assistant professor of pediatrics at the University of Cincinnati College of Medicine.

"For me, this is whether this is research and you need IRB oversight, or whether this is the practice of medicine," Corsmo says.

Distinguishing between research and innovative and/or medical care is tough in the area of surgical technique, he notes.

"It's not regulated by an outside entity, and it naturally requires some level of flexibility during the procedure," he says. "When you start a surgery, you may not know exactly what will happen when you get going."

Studies that involve devices regulated by the FDA need IRB approval, Corsmo says.

Other activities are less black and white. For instance, comparative effectiveness analyses might require an IRB review, depending on what is in the study. If the intention is to compare approved interventions to determine which one would be more effective, then it could be an expedited review, Corsmo says.

"It depends on how much control the investigator is planning to exert through the study, and which intervention they use," he adds.

Intent also is an issue. This might require trust in what physicians say they intend to do with the surgery or activity, he adds.

"When they did this surgery and came up with a new approach, was it purely out of the need to take care of that patient, or are they going into a surgery or set of surgeries with the idea of 'I have an idea and want to evaluate how it works?'" Corsmo says. "That intentionality drives whether or not they are doing research or patient care, and you have to have that trust in what the person is doing."

The only way to divine a physician's intent is to ask. "You have to have a conversation with them and ask what their intent is," Corsmo says. "You could spend a lot of time trying to catch the bad actor, but I think you have to trust your skills as an administrator or compliance person and just have that conversation with the individual to understand what their intent is."

One obvious red flag would be this type of answer: "I have this new technique, and I'm going to use it on the next five patients."

"That doesn't sound like someone who is making an independent decision to do what's in the best interest of each individual patient," Corsmo says. "It would lend itself more toward a scientific investigation, which would need, potentially, an IRB review."

It would be challenging for a research organization to create steadfast rules to separate research from medical care or innovative care. But some research medical centers might have a surgical innovations committee, he notes.

An innovations committee might participate in academic or peer discussions about innovative techniques and could speak with surgeons, suggesting they talk to IRBs, as needed.

"We don't have that at our institution, but we have a very open IRB office and frequently have

conversations like that with people," Corsmo says.

IRBs also might have a say in what is standard of care vs. an investigational activity.

"The IRB, as part of its review, will ask or have to evaluate what is the standard of care at our institution and in this discipline," Corsmo says. "We haven't had circumstances with contentious issues in trying to assess what is the standard of care."

In addition to being involved in decisions about what is research, what is standard of care, and what is innovative care, IRBs also might be involved in educating inexperienced researchers and medical residents in these differences.

"As part of the orientation that our residents get, there is a presentation module they take about what is research," Corsmo explains. "It addresses the circumstances and references of when someone might be crossing the line of clinical care into research. Most of our residents will be actively involved in a research project, so it's not necessarily foreign to them — as it's part of their training." ■

Overcoming Bots and Trolls in Research on Social Media

Quoting Twitter in research can violate privacy of posters

Social science research using Twitter to gather attitudinal and behavioral data must account for bots and trolls but can still render meaningful results, says **David Broniatowski**, PhD, FPsyS, assistant professor of systems engineering at George Washington University in Washington, D.C.

To help researchers accomplish this, Broniatowski and colleagues published a guide to identify and deal with the assorted "malicious actors," including bots, spambots, content polluters, fake followers, and human trolls.[1,2]

In previous research on the safety of vaccines, Broniatowski found that social media has become a battlefield of divisive rhetoric, some of it posted just to create the illusion of a "debate" and keep people divided. To establish this false equivalency, some tweets from the same sources have posted both negative and positive messages about vaccines, he found.[2]

Given the potential to undermine the data collected, should social science researchers simply avoid Twitter? "No, I don't think that is necessary," he tells *IRB Advisor*. "Twitter is still a rather useful tool to assess attitudes and behaviors — with the caveat that anything that you do on social media is subject to any of the distortions that come with the medium. I think every medium has its own possibilities for distortion."

> "ONE OF THE THINGS THEY PROPOSE IS IN RESEARCH INVOLVING TWITTER DATA, RESEARCHERS SHOULD CONSIDER PARAPHRASING TWEETS RATHER THAN USING THEM VERBATIM."

Twitter in particular can amplify misinformation within its open platform.

"In a sense, it is like doing social science research in a crowd and someone is holding a megaphone," he says. "That doesn't mean you can't ask everybody else their opinions. You can look at their opinions and get useful information. But the person with the megaphone is going to have an outsized influence, and you want to try to control for that."

Typical bots that imitate human messages are more likely to attack Twitter, while spambots linked to advertising show up on media like Facebook, he explains.

"Depending on how you are doing your analysis, you may not be able to completely remove the effects of Twitter bots," he says. "But it's not as if these bots in and of themselves exist in a vacuum. In many cases, they may be retweeting messages that were generated by human beings or vice versa."

As these trends continue, more IRBs may become directly involved in providing oversight for research using social media.

"We have thought a lot about that," he says. "The real question there comes down to who are the

at-risk populations? When those populations are at risk, what can be done to mitigate that consistent with IRB laws?"

For example, he cites a recent paper written by a colleague that found that quoting Twitter messages verbatim in research could result in deidentification that could violate the privacy of those quoted.

"It's often possible to reverse-identify the accounts that generate those tweets," he says. "That is problematic. One of the things they propose is in research involving Twitter data, researchers should consider paraphrasing tweets rather than using them verbatim."

In the study[3] in question, researchers reviewing a series of research articles using Twitter found that 72% quote at least one participant's tweet. Searching for the quoted content led to an identified participant 84% of the time. Moreover, 21% of the articles made a participant immediately identifiable by citing their Twitter username.

"Only one article reported obtaining consent to disclose identifying information, and institutional review board involvement was mentioned in only 40% of articles, of which 17% received IRB-approval and 23% were deemed exempt," the authors concluded.

The authors recommended that researchers aggregate findings to protect participant identities, noting that editors should reject papers that refuse to do so. IRBs should be vigilant for these issues in overseeing research that includes social media.

"It is imperative that we protect participant privacy even in social media studies," the authors noted. "First, privacy settings are set by the account owner who may post sensitive information and then later delete or make their post private. There are documented cases of people compromising their job, college admission, or relationships when their postings were rebroadcast on other media channels." ■

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OHRP Explains What to Do About Expedited Reviews

FAQs have new questions on compliance dates

IRB Advisor asked **Irene Stith-Coleman**, director of the division of policy and assurances at the Office for Human Research Protections (OHRP) in Washington, DC, to answer questions about recent OHRP guidance related to the revised Common Rule and the recent frequently asked questions (FAQs) in the following interview:

IRB Advisor: The FAQs state: "However, the first set of revisions to the 1998 list as contemplated in this commitment has not occurred yet." Would you please explain what has changed for 2019 with expedited review per the revised Common Rule? Specifically, are IRBs/research institutions in a holding pattern on expedited review changes until the U.S. Department of Health and Human Services (HHS) evaluates the list of research activities eligible for expedited review? *(http://bit.ly/2CUSZe4)*

Stith-Coleman: There exists a "holding pattern" in terms of changes to the list but not in terms of using the list. IRBs and research institutions may use the expedited review procedure, as provided for in 45 CFR 46.110(b); i.e., an IRB may use the expedited procedure to review the following:

- some or all of the research on the HHS secretary's established list of categories of research that may be reviewed by an IRB through an expedited review procedure;
- minor changes in research previously approved during the period for which approval is authorized;
- research for which IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

The context of that statement in the above-cited FAQ is the following:

• The 2018 requirements at 45 CFR 46.109(f)(1)(i) eliminate the continuing review requirement for research that is eligible for expedited review unless an IRB determines otherwise.

• Reference in 45 CFR 46.109(f)(1)(i) of the 2018 requirements to "research eligible for expedited review" refers to research that appears on the 1998 list since the list has not yet been evaluated. The 2018 requirements include a commitment for the HHS secretary to evaluate the list of research activities eligible for expedited review at least every eight years, and to amend it, as appropriate.

• Research that is subject to the 2018 requirements and that is eligible for expedited review, including research that falls into categories 8(b) or 9 of the 1998 list, would not require continuing review unless an IRB determines otherwise.

• However, OHRP recommends that IRBs use their discretion "to determine otherwise" under 45 CFR 46.109(f)(1) of the 2018 requirements to determine that continuing review of studies that are subject to these requirements and that meet the criteria for expedited review categories 8(b) or 9 should be conducted at the same frequency as required in the pre-2018 requirements; that is, at intervals appropriate to their degree of risk, but not less than once per year (pre-2018 requirements at 45 CFR 46.109(e)).

IRB Advisor: Regarding your eight new FAQs on the revised Common Rule: Why were the three newest questions about the compliance date added? Were these questions created to address issues IRBs/research institutions have often raised since the new Common Rule was published? *(The FAQs can be found at: https://bit.ly/2IeMTtt.)*

Stith-Coleman: These new questions and answers were added because of the volume of queries from the research community. OHRP does not have evidence that there has been a significant increase in compliance issues.

• What is the general compliance date of the revised Common Rule and what does it mean? OHRP answers, in part: "The compliance date of the 2018 Common Rule remains Jan. 21, 2019. This means that HHS-conducted or supported research initiated on or after Jan. 21, 2019, will need to comply with the revised Common Rule."

• If the IRB discussed a study before Jan. 21, 2019, but did not approve the study until after Jan. 21, 2019, may that study be conducted under the pre-2018 Common Rule?

OHRP's short answer is "no." Expanding on that answer, OHRP says, "If an IRB discussed a study before Jan. 21, 2019, but did not approve the study (either as submitted without any conditions, or with conditions, as described in OHRP's 'Approval of Research with Conditions' guidance document) before Jan. 21, 2019, then the study is subject to the revised Common Rule once approved."

• If an IRB approves a study with conditions before Jan. 21, 2019, but verification that the conditions are satisfied occurs after Jan. 21, 2019, is that study subject to the pre-2018 Common Rule?

OHRP responds: "As per OHRP's guidance on 'Approval of Research with Conditions,' the date the IRB approves the research with conditions is the date of IRB approval. The effective date of the IRB's approvals is the date that is verified that the investigator has satisfied all conditions related to the approval. That is also the date on which the research may actually begin. The IRB is not required to verify that the conditions are satisfied; this verification may be completed by anyone who has been designated by the IRB to do so." ■

Was There Really Support for Single IRB Approach?

It is no secret that there has been conspicuous lack of enthusiasm in some corners for the switch to a single IRB overseeing studies with multiple sites, which takes effect next year with the new Common Rule.

How did we get here? To answer this question, researchers reviewed the public comments submitted on the proposal for single-IRB review. They reviewed hundreds of comments on the question when it was originally broached in 2011 and then again in the 2015 Notice of Proposed Rulemaking.

"Our analysis indicates that support for the single-IRB mandate was limited," they reported. "The most common argument against the proposed mandate came from those concerned with the loss of site-specific IRB review of the protocol for a multisite study to address issues relevant to local context."

Although the water appears to be well under the bridge on this, we asked for comment from lead

author **Holly Taylor,** PhD, MPH, a professor in the Berman Institute of Bioethics at Johns Hopkins University in Baltimore.

IRB Advisor: In reviewing the public comments submitted to the original and revised proposal for mandated single-IRB (sIRB) review, you found a surprising lack of support for this concept. Can you comment on why there was some concern of replacing one "inefficient system" with another one?

Taylor: On the latter question, the concern is that — at least in the short-term — institutions will need to continue all the ancillary reviews conducted by their HRPPs [human research protection programs] and create new systems to manage becoming a sIRB or rely on another IRB. There seems to be consensus that the current system has inefficiencies, but not evidence that moving to the sIRB will relieve HRPPs of administrative activities.

IRB Advisor: Can you elaborate on the concern by many that use of a single IRB for a multisite study might diminish the local context of the research? Was there a concern that the results would be of less value to local researchers and research subjects?

Taylor: My sense was that the concern is about losing information that may be unique to the local setting in which the research will be conducted. I don't think this is a concern for the average multisite clinical trial where a condition or disease is the primary eligibility criteria (e.g., large oncology trial) that draw patients from a wide geographic area around the institution recruiting subjects.

The concern is about trials that will be conducted in a local community around the institution where there may be some local knowledge relevant to the recruitment of subjects that an IRB in another city or state would not be aware of. That said, in these cases the sIRB would likely realize that soliciting local input would be important and may be an exception to the general rule where local input is less important.

IRB Advisor: You and colleagues note that the "the new policy is essentially an unfunded mandate for an IRB to assume additional administrative responsibilities." Do you anticipate some reluctance to take on the single-IRB role and ensuing costs?

Taylor: That is hard to say. I think it will be hardest for smaller institutions with a smaller research "footprint" to find the resources needed. ■

REFERENCE

1. Taylor HA, Ehrhardt, Ervin AM. Public Comments on the Proposed Common Rule Mandate for Single IRB Review of Multisite Research. *Ethics Hum Res*. 2019 Jan;41(1):15-21. doi: 10.1002/eahr.500002.

Ethics of Genetic Research on Alcohol Addiction

Genetic testing is not yet ready for use in the prediction of alcohol dependence, according to recent ethical guidance.[1]

"The guidelines had a dual focus," says lead author **Audrey R. Chapman**, PhD, a Healey professor of medical ethics and humanities at UConn Health in Farmington, CT.

The authors set out to:

• identify the ethical issues and requirements related to carrying out genetic research on addiction;

• specify the ethical, legal, and public policy implications of the interpretation, translation, and application of this research.

"There is a need to guard against genetic research being misunderstood and misused," says Chapman.

The goal is to contribute to more ethically sensitive research and more socially responsible policies. For example, the potential for stigmatization carries implications not just for the individual but also family members.

"Yet there has been little literature exploring the ethical requirements of this research and its implications for public policy," says Chapman.

A better understanding of the genetic contributions to addiction could lead to more effective treatment. This could lead to the development of drugs with fewer adverse side effects. There also is the hope that genotyping could better match patients to existing pharmacological treatments for addiction."These hopes have fueled medical investments in this field of research," says Chapman.

The guidelines identify the limitations of this paradigm. "Alcohol dependence is a complex, multifactorial polygenic disorder," notes Chapman. Evidence suggests it is unlikely that one or even a small number of genes will be identified that explain all the variance in heritability. "Hopefully, the guidelines will help shape future research on the genetic dimensions of alcohol dependence," she says. ■

REFERENCE

1. Chapman AR, Carter A, Kaplan JM, et al. Ethical guidelines for genetic research on alcohol addiction and its applications. *Kennedy Inst Ethics J*. 2018; 28:1-22.

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CME/CE QUESTIONS

1. **A World Health Organization panel formed in the wake of highly controversial human embryo research in China called for:**

   a. criminal prosecution of those gestating edited embryos.
   b. a central registry on human genome editing research.
   c. allowing gene-edited embryos for those with high risk of disease.
   d. creating a central research base where all gene-editing trials would be conducted.

2. **According to Central Michigan University's compliance office, which of the following is information that research recruitment advertisements must include?**

   a. Summary of eligibility criteria
   b. List of all potential adverse events
   c. Summary of outcomes from similar studies
   d. List of all blood draws and other procedures

3. **The Office for Human Research Protections says an IRB may use an expedited procedure to review a study for which of the following reasons?**

   a. The research is on the FDA's list of categories of research approved for expedited review.
   b. Minor changes in research previously approved during the period for which approval is authorized.
   c. IRB has received a broad exemption in requiring reviews for this specific type of research.
   d. Study previously was on continuing review but now qualifies for exempted review due to regulatory changes from the 21st Century Cures Act.

4. **Robert Klitzman, MD, said which of the following countries allow the sale and purchase of human eggs?**

   a. India
   b. China
   c. Germany
   d. Brazil